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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,184	03/05/2002	John H. Lawrence III	47746-C	1657

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,184	LAWRENCE ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/10/02*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,27,28,37-39,47,48,52-56 and 61-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,5,27,28,37-39,47,48,52-56 and 61-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *3//5/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

Claims 6-26, 29-36, 40-46, 49-51, 57-60 have been canceled by the preliminary amendment filed March 5, 2002, claims 61-75 have been added by the amendment filed November 10, 2004. Applicant's election of the species vascular endothelium factor, the species heart cell and the species human in the amendment dated November 10, 2004 is acknowledged.

However, due to applicant's amendment to the claims, only the species restriction of heart cells from other types of cells is currently remaining in effect.

The specification is also objected because the status of the parent applications in the cross-reference information, which appears in the first paragraph of the specification, must be updated so as to reflect that this application is claiming priority under 35 USC 120 to the parent 09/169,739 application which was issued as US patent 6,376,471.

Claims 1-2, 5, 27-28, 37-39, 47, 48, 52-56, 61-75 are pending for examination.

Claims 1, 5, 27, 37, 47, 52, 61 are objected because the "exogenous nucleic acid" lack the article "an". Also, claim 62 lacks the article "a" immediately in front of "calcium ion concentration". Clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 27, 37-39, are readable on a genus of treating step(s) and/or material(s) in order to exhibit applicant's contemplated desire of increasing vascular permeability of an exogenous nucleic acid. The main thrust of the invention, when read in light of the as-filed specification, is the concept of using a vascular permeability agent and/or an calcium ion concentration of from about 40 umol/L to about 500 umol/L. The as-filed specification does not provide any description of a representative number of other species of method treating steps and/or materials in order to increase vascular permeability of an exogenous nucleic acid. Thus, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential method treating steps and/or material(s) for the claimed genus; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of treatment steps and/or materials thereof that must exhibit the disclosed biological functions as contemplated by the as-filed specification.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming a genus of treating step(s) and/or unspecified materials that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli*

Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed treating steps that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1, 27, 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A method for administering a nucleic acid to express a gene product in cells in tissue of interest, comprising:

Treating the tissue with a vascular permeability agent so as to increase vascular permeability of an exogenous nucleic acid; and

administering the exogenous nucleic acid to the tissue.

The specification does not reasonably provide enablement for the presently pending claims The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of the genus of treating step(s) and/or unspecified materials as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention as broadly claimed. Also, claim 5, for example, recites that claimed invention can be broadly claimed as to treat a target tissue with a vascular permeability agent under conditions of low calcium concentration to increase vascular permeability of an exogenous nucleic acid. Likewise, claims 61 and 62, for example, claim that an exogenous nucleic acid can be administered under a calcium ion concentratin of abouit 500 umoll/L or less. However, a close review of the as-filed application, the only conditions that can be reasonably envisioned and understood by a skilled artisan in an application of a

treatment solution comprising an exogenous nucleic acid, a vascular permeability agent, and/or a calcium ion concentration of about 500 umol/L or less. Given that the as-filed specification does not appear to teach any other meaningful way to carry out the invention so as to achieve applicant's contemplated function, the claims are only reasonably enabling for claimed embodiments as indicated in the enabling paragraphs.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 52, 53, 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 52, 53, 55 are indefinite in the recitation of "low" because "low" is relative in meanings and does not indicate *per se* as to what is exactly the standard or point of reference for determining the metes and bounds of the "low calcium ion concentration".

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 47, and 52 are rejected under 35 U.S.C. 102(a) as being anticipated by Fasano (WO 96/37196).

Fasano teaches a method of employing a capsule containing zonula occludens toxin as a vascular permeability agent and a nucleic acid containing an attenuated viral DNA for to enhance tissue permeability of the nucleic acid (pages 10, 13, and 16).

Absent evidence to the contrary, the kits and/or the treatment solution of Fasano and the nucleic acid delivery method of Fasano have all of the properties cited in the claims.

Claims 1, 2, 47, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolff (US Pat No. 6,265,387).

Wolff teaches a method of employing a vascular permeability agent such as VEGF to enhance the permeability of a blood vessel within the target tissue, thereby increasing the efficiency of the polynucleotide delivery and expression (column 6 through column 7). The patent as a whole teaches numerous kits and/or treatment solutions comprising a vascular permeability agent and a nucleic acid vector.

Thus, Wolff anticipates the claims.

Claims 1, 2, 37, 47, and 52 are rejected under 35 USC 102(e) as being anticipated by Ryan (US 2003/0195495 A1)

Ryan teaches on page 8 a concept of employing a combination of vascular endothelial growth factor, vascular permeability factor, and a gene therapy encoding a VEGF so as to increase permeability, proliferation of vascular endothelial cells, and perfusion and/or delivery of the agents to the cells. Catheter kit comprising these agents are disclosed. In addition, page 8 discloses that donor endothelial cells can be cultured so as to increase the delivery and/or transport and/or permeability of a nucleic acid vector into the cultured cell, and that the cultured and transfected cells can be implanted into a treated subject.

Thus, Ryan anticipates the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 27, 28, 47, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nabel *et al.* (US Pat No. 5,328,47) taken with Wolff, Epstein *et al.* (US Pat No. 6,007,817) or Neufeld *et al.* (US Pat No. 6,013,780).

Nabel *et al.* teach a nucleic acid delivery kit comprising a catheter and a DNA composition comprising a DNA encoding a toxin, and a method of employing the kit for delivering a DNA to a target tumor cells in blood vessels *in vitro* and/or *in vivo* (entire document, column 12, lines 34-37, column 14). More specifically, column 13 discloses that a targeting ligand is complexed to the DNA and that a carrier is coupled to the DNA for enhancing the delivery of the DNA to the target cell. Nabel *et al.* do not teach that a vascular permeability agent is employed in the DNA kit so as to enhance the delivery of the DNA to the target tumor cell.

However, at the time the invention was made, Wolff, Epstein *et al.* or Neufeld *et al.* teach a method of employing a vascular permeability agent (Wolff, columns 6, 7; Epstein *et al.,* IL-2; Neufeld *et al.,* VEGF) for enhancing the delivery of a bioactive molecule to target tumor cells (Epstein *et al.,* columns 3, claim 1; Neufeld *et al.,* column 6).

It would have been obvious for one of ordinary skill in the art to have modified the DNA delivery method Nabel *et al.* by employing a vascular permeability agent so as to enhance the delivery of the DNA to target tumor cells. One of ordinary skill in the art would have been motivated to have employed any known vascular permeability agent in the exemplified DNA delivery method Nabel *et al.* because Wolff, Epstein *et al.* or Neufeld *et al.* teaches that vascular permeability agents can be used in a method of delivering a bioactive drug to a tumor cell so as to enhance the delivery of the bioactive drug to the tumor cell.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ryan taken with Wolff, Epstein *et al.* (US Pat No. 6,007,817) or Neufeld *et al.* (US Pat No. 6,013,780).

Ryan teaches on page 8 a concept of employing a combination of vascular endothelial growth factor, vascular permeability factor, and a gene therapy encoding a VEGF so as to increase permeability, proliferation of vascular endothelial cells, and perfusion and/or delivery of the agents to the cells. Catheter kit comprising these agents are disclosed. In addition, page 8 discloses that donor endothelial cells can be cultured so as to increase the delivery and/or transport and/or permeability of a nucleic acid vector into the cultured cell, and that the cultured and transfected cells can be implanted into a treated subject. Ryan does not teach explicitly that a vascular permeability agent is employed in the culturing conditions would include an application of a vascular permeability agent so as to enhance the delivery of the DNA into the cultured cells..

However, at the time the invention was made, Wolff, Epstein *et al.* or Neufeld *et al.* teach a method of employing a vascular permeability agent (Wolff, columns 6, 7; Epstein *et al.,* IL-2; Neufeld *et al.,* VEGF) for enhancing the delivery of a bioactive molecule to target cells (Epstein *et al.,* columns 3, claim 1; Neufeld *et al.,* column 6).

It would have been obvious for one of ordinary skill in the art to have modified the DNA delivery method of Ryan by employing a vascular permeability agent so as to enhance the delivery of the DNA to target cells *ex vivo*. One of ordinary skill in the art would have been motivated to have employed any known vascular permeability agent in the exemplified DNA delivery method Ryan because Wolff, Epstein *et al.* or Neufeld *et al.* teaches that vascular permeability agents can be used in a method of delivering a bioactive drug to a target cell so as to enhance the delivery of the bioactive drug to the tumor cell.

Thus, the claimed invention as a whole was *prima facie* obvious.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 5, 27-28, 47, 48, 52-56, 61-75 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-50 of U.S. Patent No. 6,376,471. Although the conflicting claims are not identical, they are not patentably distinct from each other because

Both the examined claims and the patent claims are embracing a treatment solution or kit comprising a vascular permeability agent that increases vascular permeability of cells to an exogenous nucleic acid, a nucleic acid; and a solution having an effective amount of a calcium ion concentration, which is aboiut 500 um/L or less. The examined and patent claims also embrace an *in vivo* delivery method by employing the treatment solution or kit.

Thus, the patent and examined claims are obvious variants of one another.

Other than the references Wolff and Ryan, which are newly cited, all other references had been cited in the parent application of this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0184.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER